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PC(InPh) 7068/A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

8/21/87

APPLICANT: P. E. CROSS ET AL :

SERIAL NO.: 044,086 : GROUP ART UNIT: 129

FILING DATE: APRIL 29, 1987 : EXAMINER: Unknown

FOR: ANTI-ARRHYTHMIC AGENTS :

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Washington, D.C. 20231

Sir:

TRANSMITTAL OF CERTIFIED COPIES

Transmitted herewith are certified copies of Great Britain Application No. 8610668 filed May 1, 1986 and Ireland Application No. 8630059 filed December 17, 1986, the above-identified application claiming priority from both applications.

Respectfully submitted

Dated: August 14, 1987

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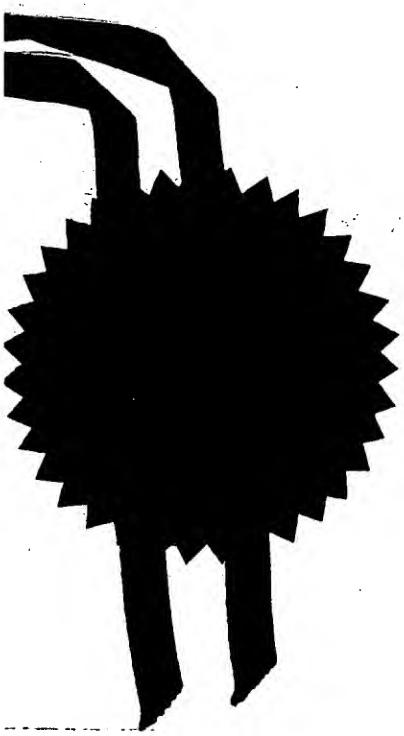
In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents, has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or the inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.



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Re-registration under the companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

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PATENTS ACT 1977

PATENTS FORM No. 1/77 (Revised 1982)
(Rules 16, 19)

1 MAY 1986

02/05/86 05170 PATENT 10.00

The Comptroller
The Patent Office
25 Southampton Buildings
London, WC2A 1AY

1986
10668

REQUEST FOR GRANT OF A PATENT
8610668

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's Reference *(Please insert if available)* PLC 428

II Title of Invention
"Anti-Arrhythmia Agents"

III Applicant or Applicants *(See note 2)*
Name (First or only applicant) PFIZER LIMITED
.....
Country United Kingdom State ..... ADP Code No. .....
Address Ramsgate Road, Sandwich, Kent, CT13 9NJ,
.....
Name (of second applicant, if more than one) .....
..... Country ..... State .....
Address .....
.....

IV Inventor (see note 3)
~~(a) The applicant(s) is/are the sole/joint inventor(s)~~
~~or~~
(b) A statement on Patents Form No 7/77~~/~~ will be furnished

V Name of Agent (if any) *(See note 4)* D.J. Wood | ADP CODE NO

VI Address for Service (See note 5)
Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ

VII Declaration of Priority (See note 6)
Country Filing date File number
.....
.....
.....
.....

VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7)
Earlier application or patent number ..... and filing date .....

V4919

IX Check List *(To be filled in by applicant or agent)*

A The application contains the following number of sheet(s)

1	Request ..... 1 ..... Sheet(s)	1	Priority document .....
2	Description ..... 25 ..... Sheet(s)	2	Translation of priority document .....
3	Claim(s) ..... ✓ ..... Sheet(s)	3	Request for Search ..... ✓ .....
4	Drawing(s) ..... ✓ ..... Sheet(s)	4	Statement of Inventorship and Right to Grant ..... ✓ .....
5	Abstract ..... ✓ ..... Sheet(s)		

B The application as filed is accompanied by:-

X It is suggested that Figure No ..... ✓ ..... of the drawings (if any) should accompany the abstract when published.

XI Signature *(See note 8)* D.J. Wood D.J. Wood

NOTES:

1. This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.
2. Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly [known as] ABC Ltd." are not required and should not be given. Also enter applicant(s) ADP Code No. (if known).
3. Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.
4. If the applicant has appointed an agent to act on his behalf, the agent's name and the address of his place of business should be indicated in the spaces available at V and VI. Also insert agent's ADP Code No. (if known) in the box provided.
5. An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.
6. The declaration of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.
7. When an application is made by virtue of section 8(3), 12(6), 15(4), or 37(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.
8. Attention is directed to rules 90 and 106 of the Patent Rules 1982.
9. Attention of applicants is drawn to the desirability of avoiding publication of inventions relating to any article, material or device intended or adapted for use in war (Official Secrets Acts, 1911 and 1920). In addition after an application for a patent has been filed at the Patent Office the comptroller will consider whether publication or communication of the invention should be prohibited or restricted under section 22 of the Act and will inform the applicant if such prohibition is necessary.
10. Applicants resident in the United Kingdom are also reminded that, under the provisions of section 23 applications may not be filed abroad without written permission or unless an application has been filed not less than six weeks previously in the United Kingdom for a patent for the same invention and no direction prohibiting publication or communication has been given or any such direction has been received.

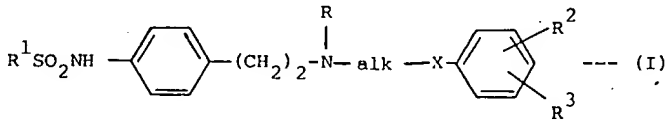
ANTI-ARRHYTHMIA AGENTS

DESCRIPTION

This invention relates to certain sulfonamides which are anti-arrhythmia agents.

The compounds of the invention prolong the duration of the action potential in cardiac muscle and conducting tissue, and thereby increase refractoriness to premature stimuli. Thus, they are Class III antiarrhythmic agents according to the classification of Vaughan Williams (Anti-Arrhythmic Action, E.M. Vaughan Williams, Academic Press, 1980). They are effective in atria, ventricles and conducting tissue both in vitro and in vivo and are therefore useful for the prevention and treatment of a wide variety of ventricular and supraventricular arrhythmias including atrial and ventricular fibrillation. Because they do not alter the speed at which impulses are conducted, they have less propensity than current drugs (mostly Class I) to precipitate or aggravate arrhythmias, and also produce less neurological side effects. Some of the compounds also have some positive inotropic activity and therefore are particularly beneficial in patients with impaired cardiac pump function.

Thus the invention provides compounds of the formula:-



and their pharmaceutically acceptable salts,

wherein R^1 is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, $-CF_3$, $-CH_2Cl$ or $-CH_2CF_3$;

R is C_1-C_4 alkyl;

X is O or S;

"alk" is an ethylene, trimethylene or tetramethylene group optionally substituted by a methyl group;

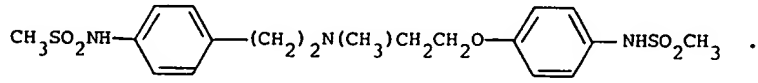
R^2 is H, halo, CF_3 or C_1-C_4 alkyl;

and R^3 is a group of the formula $-NHSO_2R^1$ where R^1 is as

defined above or $-CONR^4R^5$ where R^4 and R^5 are each independently H or C_1-C_4 alkyl or together with the nitrogen atom to which they are attached represent a 1-pyrrolidinyl, piperidino, morpholino or N-methylpiperazin-1-yl group.

"Halo" means F, Cl, Br or I. C_3 and C_4 alkyl groups can be straight or branched chain. "Alk" is preferably $-(CH_2)_n-$ where n is 2, 3 or 4, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)CH_2CH_2-$ or $-CH_2CH_2CH(CH_3)-$.

A preferred individual compound has the formula:-



The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, benzoate, methanesulphonate, besylate and p-toluenesulphonate salts. The compounds also form metal salts, preferred examples of which are the alkaline earth and alkali metal salts. The sodium and potassium salts are most preferred. The salts are preparable by conventional techniques.

For assessment of effects of the compounds on atrial refractoriness, guinea pig right hemiatria are mounted in a bath containing physiological salt solution, and one end is connected to a force transducer. Tissues are stimulated at 1 Hz using field electrodes. Effective refractory period (ERP) is measured by introducing premature stimuli (S_2) after every 8th basic stimulus (S_1). The S_1S_2 coupling interval is gradually increased until S_2 reproducibly elicits a propagated response. This is defined as the ERP. The concentration of compound required to increase ERP by 25% (ED_{25}) is then determined. ERP is also measured in guinea pig right papillary muscles incubated in physiological salt solution. Muscles are stimulated at one end using bipolar electrodes and the propagated electrogram is recorded at the opposite end via a unipolar surface electrode. ERP is determined

as above using the extrastimulus technique. Conduction time is obtained from a digital storage oscilloscope by measuring the interval between the stimulus artefact and the peak of the electrogram (i.e. the time required for the impulse to travel along the length of the muscle).

Atrial and ventricular ERP's are also measured in anaesthetised or conscious dogs by the extrastimulus technique whilst the atrium or right ventricle is being paced at a constant rate.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. They can be administered both to patients suffering from arrhythmias and also prophylactically to those likely to develop arrhythmias. For example they may be administered orally in the form of tablets containing such excipients as starch of lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

For administration to man in the curative or prophylactic treatment of cardiac conditions such as ventricular and supraventricular arrhythmias, including atrial and ventricular fibrillation, it is expected that oral dosages of the compounds of the invention will be in the range from 1 to 75 mg daily, taken in up to 4 divided doses per day, for an average adult patient (70 kg). Dosages for intravenous administration would be expected to be within the range 0.5 to 10mg per single dose as required. A severe cardiac arrythmia is preferably treated by the i.v. route in order to effect a rapid conversion to the normal rhythm. Thus for a typical adult patient individual tablets or capsules might for example contain 1 to 25mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Variations may

occur depending on the weight and condition of the subject being treated as will be known to medical practitioners.

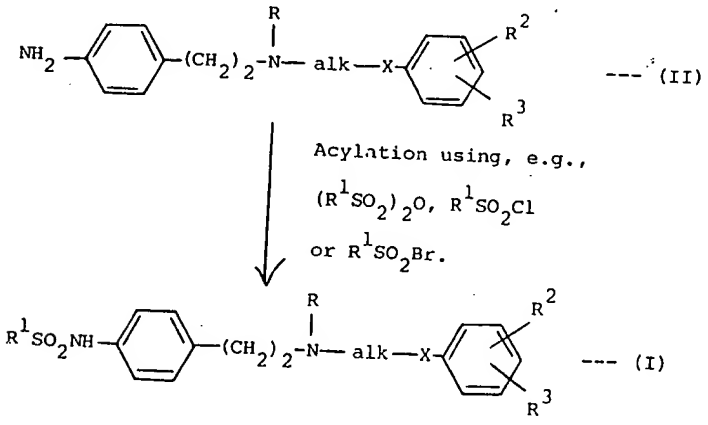
Thus the present invention provides a pharmaceutical composition comprising a compound of the formula (I) as defined above or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of preventing or reducing cardiac arrhythmias in a human being, which comprises administering to said human an effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as defined above.

The invention yet further provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament, particularly as an anti-arrhythmia agent.

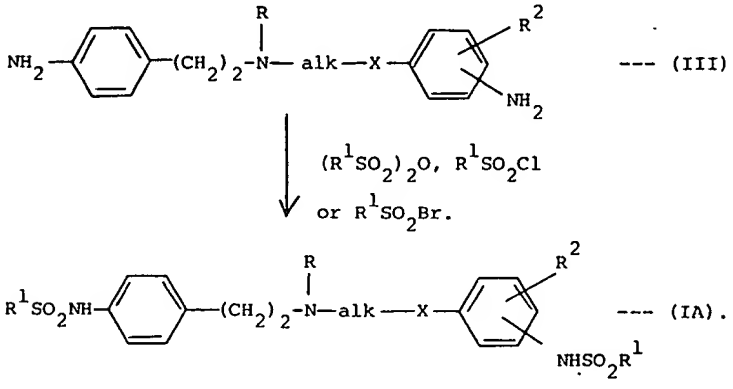
The invention also provides the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prevention or reduction of cardiac arrhythmias.

The compounds of the formula (I) can be prepared by the following general route, in which R, R^1, R^2, R^3, alk and X are as defined for formula (I):-



The reaction is typically carried out in a suitable organic solvent, e.g. methylene chloride, at room temperature. It is preferred to use the sulphonic anhydride $(R^1SO_2)_2O$ or sulphonyl chloride R^1SO_2Cl as the sulphonylating agent. The product (I) can then be isolated and purified by conventional techniques.

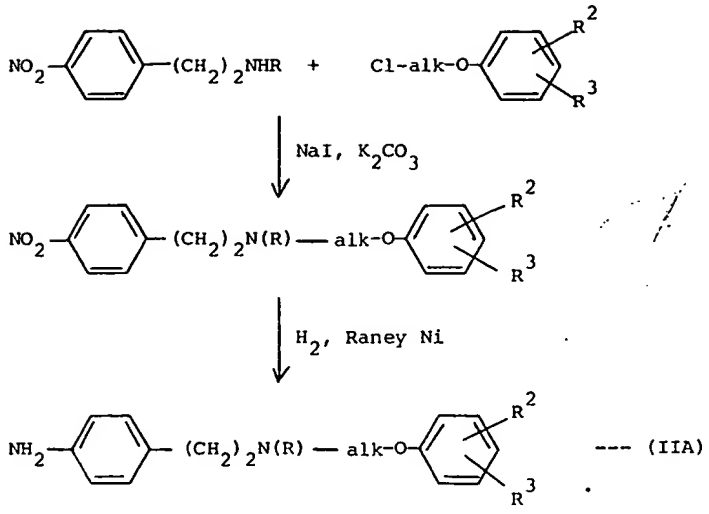
When R^3 is $-NHSO_2R^1$, then the following route, starting from a compound in which R^3 is $-NH_2$, is preferred:-



The reaction can again be carried out in a suitable organic solvent, e.g. methylene chloride, at room temperature, although at least 2 equivalents of the sulphonylating agent must of course be used and, in the end product (IA), each R^1 will be the same.

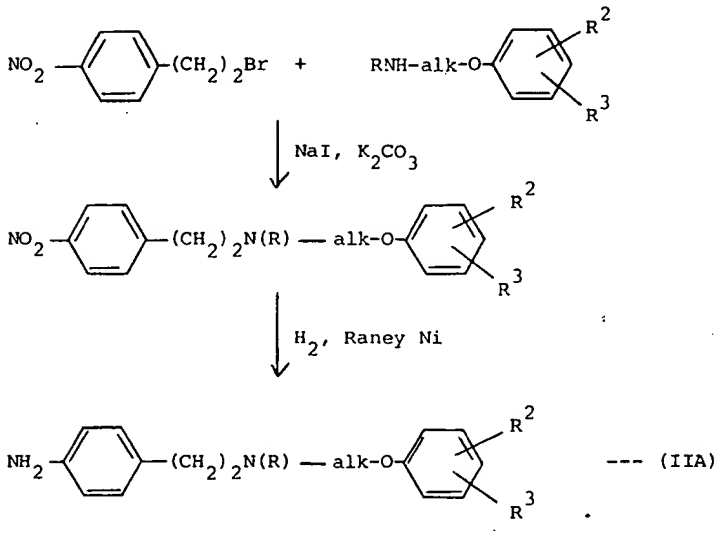
The starting materials for the above routes are obtainable by conventional methods, e.g. as follows:-

(a)


NO2
(CH2)2NHR
+
Cl-alk-O
R2
R3
NaI, K2CO3
NO2
(CH2)2N(R)
alk-O
R2
R3
H2, Raney Ni
NH2
(CH2)2N(R)
alk-O
R2
R3

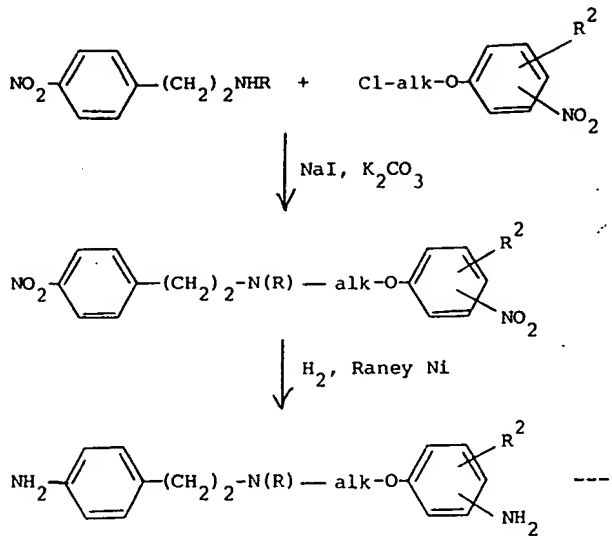
--- (IIA)

(b)


NO2
(CH2)2Br
+
RNH-alk-O
R2
R3
NaI, K2CO3
NO2
(CH2)2N(R)
alk-O
R2
R3
H2, Raney Ni
NH2
(CH2)2N(R)
alk-O
R2
R3

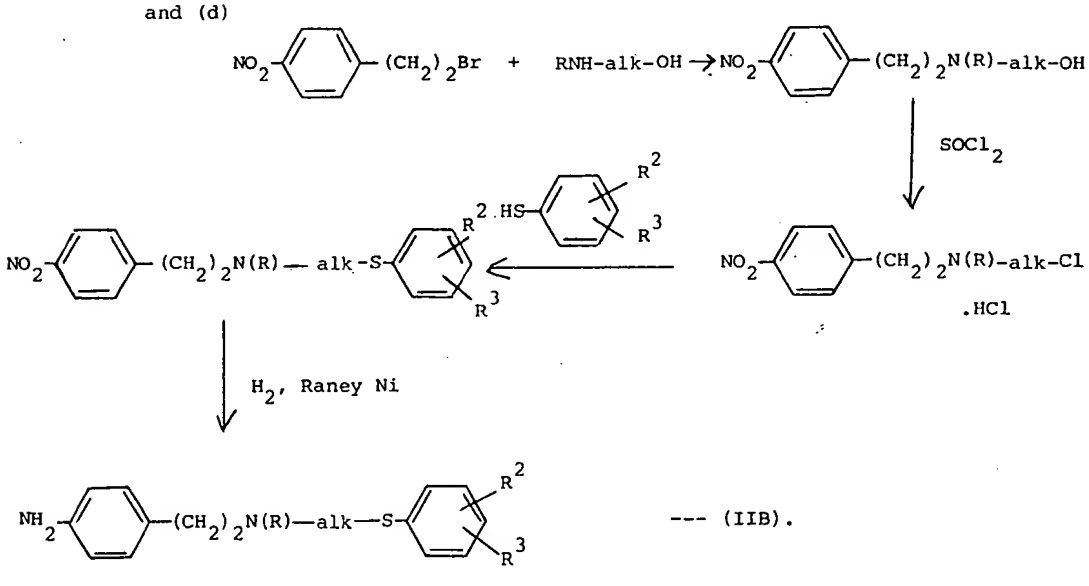
--- (IIA)

(c)



--- (IIIA)

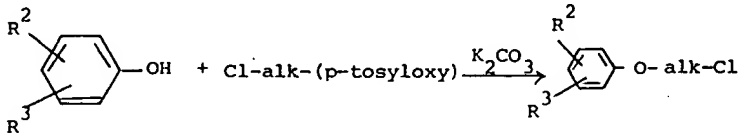
and (d)

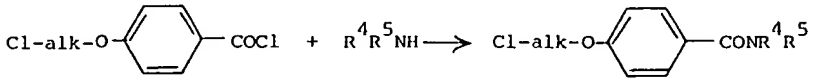


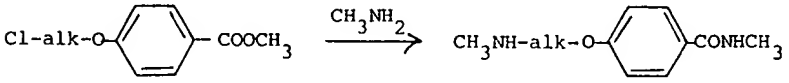
--- (IIB).

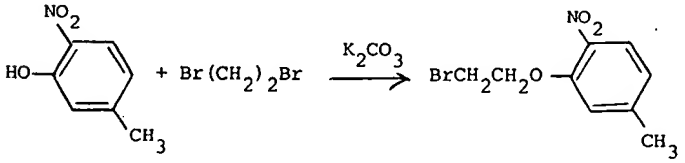
In a modification of this scheme, a thiol in which R^3 is nitro can be used. The hydrogenation step will also reduce this nitro group to amino [cf. route (c) above], thus producing an intermediate of the structure (IIB) having R^3 as amino.

Where the starting materials used in (a), (b) and (c) above are not known compounds, they can again be prepared by conventional techniques, e.g. as follows:-

(i) 

(ii) 

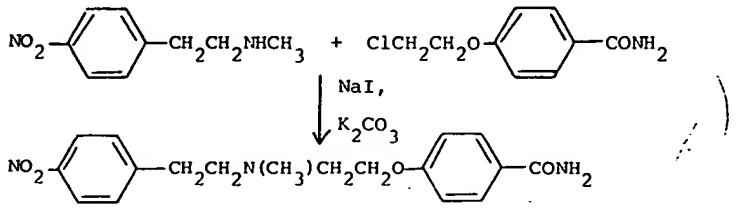
(iii) 

or (iv) 

The following Examples, in which all temperatures are in °C, illustrate the invention:-

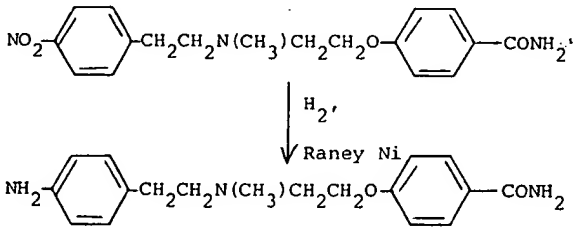
EXAMPLE 1

(A) 4-{2-[N-Methyl-N-(4-nitrophenethyl)amino]ethoxy}benzamide



To a solution of N-methyl-4-nitrophenethylamine (1.8 g) [J.O.C., (1956), 21, 45] and 4-(2-chloroethoxy)benzamide (C.A., 94, 15731d) in acetonitrile (100 ml) was added potassium carbonate (3.0 g) and sodium iodide (1.5 g) and the suspension stirred at reflux for 72 hours. After evaporation, a 2N aqueous sodium bicarbonate solution was added to the residual oily solid and then extracted three times with methylene chloride. The combined organic layers were washed with a saturated aqueous brine solution, dried over magnesium sulphate, filtered and evaporated to give a yellow oil. Trituration of the oil with diisopropyl ether gave 2.3 g of a yellow solid which was crystallised from toluene to give the title compound (1.4 g), m.p. 116-118°, which was used directly without further purification.

(B) 4-{2-[N-(4-Aminophenethyl)-N-methylamino]ethoxy}benzamide

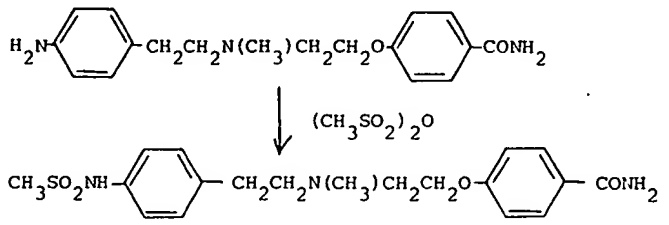


A solution of 4-{2-[N-methyl-N-(4-nitrophenethyl)amino]-ethoxy} benzamide (1.4 g) in ethanol (100 ml) was stirred for 16 hours at room temperature under three atmospheres of hydrogen in the presence of Raney nickel ("Nicat 102", Trade Mark). The reaction mixture was filtered and evaporated to dryness to give a yellow solid (1.2 g) which crystallised from ethyl acetate to give the title compound, (1.1 g), m.p. 110-112°.

Analysis %:-

Found:	C,69.1; H,7.3; N,13.05;
Calculated for $C_{18}H_{23}N_3O_2$:	C,69.0; H,7.4; N,13.40.

(C) 4-{2-[N-Methyl-N-(4-methanesulphonamidophenethyl)amino]-ethoxy}benzamide



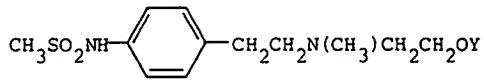
A solution of 4-{2-[N-(4-aminophenethyl)-N-methylamino]-ethoxy}benzamide (1.0 g) and methanesulphonic anhydride in dry methylene chloride (50 ml) was stirred at room temperature for 16 hours. After evaporation a 2N aqueous sodium bicarbonate solution was added to the residue followed by extraction three times with methylene chloride. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give a light brown solid. Crystallisation from toluene/ethyl acetate gave the title compound (0.31 g), m.p. 147°.

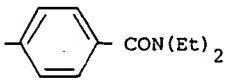
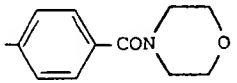
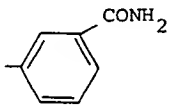
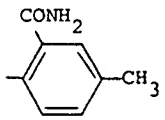
Analysis %:-

Found:	C,58.35; H,6.7; N,10.45;
Calculated for $C_{19}H_{25}N_3O_4S$:	C,58.3; H,6.4; N,10.7.

EXAMPLES 2 TO 5

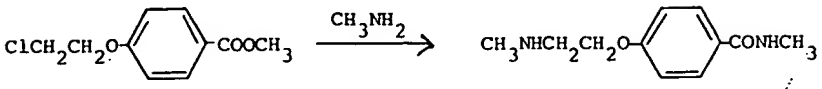
The following compounds were prepared similarly to Example 1 parts (A) to (C) from appropriate starting materials. In Examples 3 and 5, the products were characterised as hydrochloride salts by adding ethyl acetate to the solid resulting from the second evaporation step in part (C), followed by treatment with ethereal hydrogen chloride, filtering off the resulting hydrochloride salt, and recrystallising it from ethyl acetate/methanol.



Example No.	Y	Form Isolated	Recrystallization Solvent	m.p. (°C)	Analysis % (Theoretical in Brackets) C	H	N
2		Free base	Diisopropyl ether/ ethyl acetate	97-98	61.7 (61.7	7.25 7.4	9.10 9.4)
3		Hydrochloride hemihydrate	Ethyl acetate/ methanol	198-201	54.96 (54.5	6.3 6.6	8.0 8.3)
4		Free base	Ethyl acetate	104-106	57.8 (58.3	6.39 6.44	10.60 10.73)
5		Hydrochloride	Ethyl acetate/ methanol	124-126	54.70 (54.3	6.7 6.4	9.1 9.5)

EXAMPLE 6

(A) N-Methyl-4-(2-methylaminoethoxy)benzamide

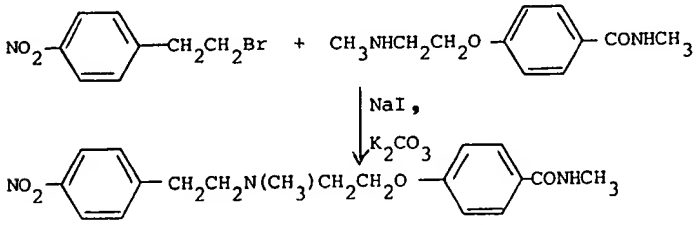


To a 33% solution of methylamine in industrial methylated spirits (50 ml) was added methyl 4-(2-chloroethoxy)benzoate (4.3 g) (DT-OS-2950019) and the mixture was stirred while heating at 100° in a 130 ml sealed pressure vessel for 16 hours. After evaporation to dryness, the resultant solid was added to 10 ml of 2N aqueous sodium hydroxide solution and extracted three times with methylene chloride. The combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated to give a colourless solid. Crystallisation from isopropanol gave the title compound, (2.1 g), m.p. 95-96°.

Analysis %:-

Found:	C,63.7; H,7.6; N,13.4;
Calculated for $C_{11}H_{16}N_2O_2$:	C,63.4; H,7.7; N,13.45.

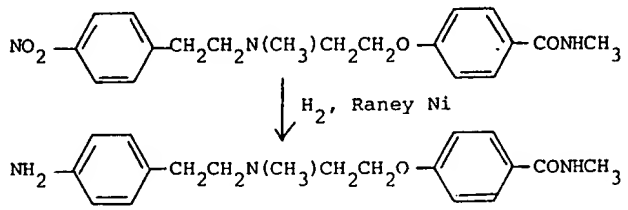
(B) N-Methyl-4-{2-[N'-methyl-N'-(4-nitrophenethyl)amino]ethoxy}-benzamide



To a solution of N-methyl-4-(2-methylaminoethoxy)benzamide and 4-nitrophenethyl bromide in acetonitrile (100 ml) was added potassium carbonate (3.0 g) and sodium iodide (1.5 g) and the suspension was stirred at reflux for 72 hours. After evaporation, a 2N aqueous sodium hydroxide solution was added followed by extraction three times with methylene chloride. The combined organic layers were washed with a saturated aqueous brine solution, dried over magnesium sulphate, filtered and evaporated to give a yellow oil. Trituration of the oil with diisopropyl ether gave the title compound as a yellow solid, (2.4 g), which was used without further purification.

N.m.r. ($CDCl_3$), ppm, δ = 7.9 (d, 2H); 7.52 (d, 2H); 7.12 (d, 2H); 6.63 (d, 2H); 3.9 (t, 2H); 2.8 (m, 9H); 2.28 (s, 3H).

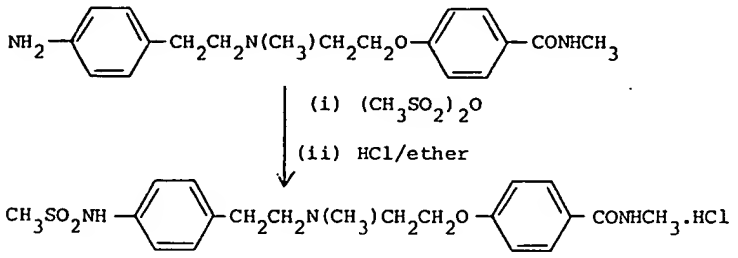
(C) N-Methyl-4-{2-[N'-(4-aminophenethyl)-N'-methylamino]ethoxy}-benzamide



A solution of N-methyl-4-{2-[N'-methyl-N'-(4-nitrophenethyl)amino]ethoxy}benzamide (2.3 g) in ethanol (100 ml) was stirred for 16 hours at room temperature under three atmospheres of hydrogen in the presence of Raney nickel ("Nicat 102" - Trade Mark). The reaction mixture was filtered and evaporated to dryness to give a yellow oil (2.1 g). Chromatography on silica ("Kieselgel 60" - Trade Mark) eluting with ethyl acetate gave the title compound as a colourless oil, (1.7 g), which was used directly without further purification.

N.m.r. ($CDCl_3$) ppm, δ = 7.72 (d, 2H); 7.0 (d, 2H); 6.92 (d, 2H); 6.62 (d, 2H); 3.0 (d, 3H); 2.88 (t, 2H); 2.7 (s, 4H); 2.42 (s, 3H).

(D) N-Methyl-4-{2-[N'-(4-methanesulphonamidophenethyl)-N'-methylamino]ethoxy}benzamide hydrochloride



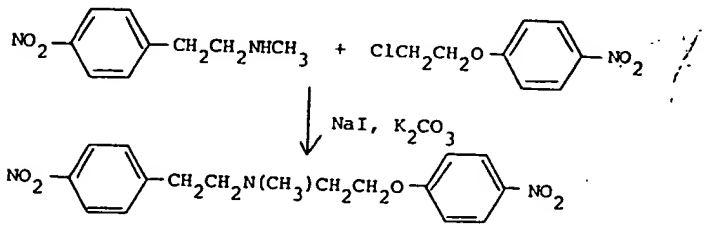
A solution of N-methyl-4-{2-[N'-(4-aminophenethyl)-N'-methylamino]ethoxy}benzamide (1.6 g) and methanesulphonic anhydride (0.87 g) in dry methylene chloride (50 ml) was stirred at room temperature overnight. After evaporation, the resultant oily solid was treated with a 2N aqueous sodium bicarbonate solution and extracted three times with methylene chloride. The combined organic layers were washed with a saturated aqueous brine solution, dried over magnesium sulphate, filtered and evaporated. Chromatography on silica ["Kieselgel 60" - Trade Mark] eluting with ethyl acetate gave a colourless oil (0.52 g). The oil was dissolved in ethyl acetate and an ethereal solution of hydrogen chloride was added until precipitation was complete. The colourless solid was filtered off and crystallised from ethyl acetate/methanol to give the title compound, (0.2 g), m.p. 160°.

Analysis %:-

Found:	C,54.2; H,6.6; N,9.25;
Calculated for $C_{20}H_{27}N_3O_4S.HCl$:	C,54.35; H,6.4; N,9.5.

EXAMPLE 7

(A) 1-(4-Nitrophenoxy)-2-[N-methyl-N-(4-nitrophenethyl)amino]-ethane

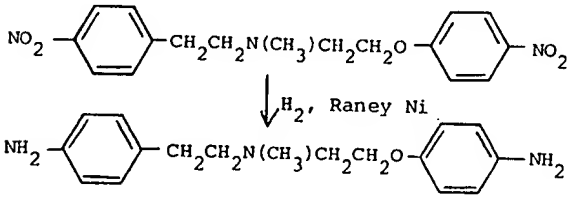


To a solution of N-methyl-4-nitrophenethylamine (1.5 g) (J.O.C., [1956], 21, 45) and 2-[4-nitrophenoxy]ethyl chloride (1.55 g) (C.A., [1965], 63, 11433f) in acetonitrile (50 ml) was added potassium carbonate (1.25 g) and sodium iodide (1.2 g) and the suspension was stirred at reflux for 72 hours. After evaporation to dryness, the residual oily solid was partitioned between a 2N aqueous sodium bicarbonate solution and ethyl acetate. After two further extractions with ethyl acetate, the organic portions were combined, washed with a saturated aqueous brine solution, dried over magnesium sulphate, filtered and evaporated. The resultant orange solid (2.7 g) was crystallised from ethanol to give the title compound, (1.9 g), m.p. 74°.

Analysis %:

Found:	C,58.75; H,5.4; N,12.15;
Calculated for $C_{17}H_{19}N_3O_4$:	C,59.1; H,5.5; N,12.2.

(B) 1-(4-Aminophenoxy)-2-[N-(4-aminophenethyl)-N-methylamino]-ethane

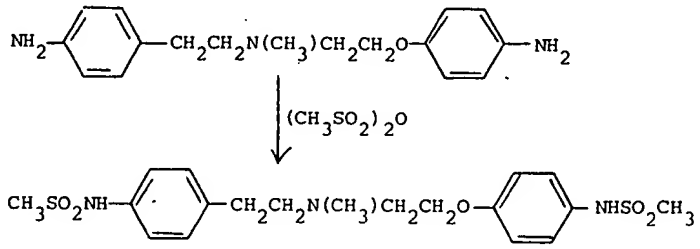


A solution of 1-(4-nitrophenoxy)-2-[N-methyl-N-(4-nitrophenethyl)amino]ethane (1.5 g) in ethanol (100 ml) was stirred for 16 hours at room temperature under three atmospheres of hydrogen in the presence of Raney nickel ("Nicat 102" - Trade Mark). The reaction mixture was filtered and evaporated to dryness. The residual oil was re-dissolved in ether, filtered and evaporated to give a yellow solid (1.1 g), which was crystallised from ethyl acetate/60-80° petroleum ether to give the title compound, (0.9 g), m.p. 73-74°.

Analysis %:-

Found:	C,71.3; H,8.1; N,14.7;
Calculated for $C_{17}H_{23}N_3O$:	C,71.55; H,8.1; N,14.7.

(C) 1-(4-Methanesulphonamidophenoxy)-2-[N-(4-methanesulphonamidophenethyl)-N-methylamino]ethane



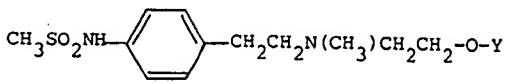
A solution of 1-(4-aminophenoxy)-2-[N-(4-aminophenethyl)-N-methylamino]ethane (0.75 g) and methanesulphonic anhydride (1.0 g) in dry methylene chloride (50 ml) was stirred at room temperature overnight. After evaporation, the resultant oil was partitioned between a 2N aqueous sodium bicarbonate solution and ethyl acetate. After two further extractions with ethyl acetate, the organic portions were combined, dried over magnesium sulphate, filtered and evaporated. The resultant colourless solid (1.2 g) was crystallised from ethyl acetate/methanol to give the title compound, (0.6 g), m.p. 147-149°.

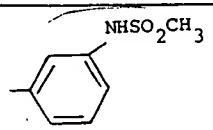
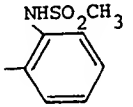
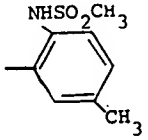
Analysis %:-

Found:	C,52.1; H,6.25; N,9.45;
Calculated for $C_{19}H_{27}N_3O_5S_2$:	C,51.9; H,6.15; N,9.4.

EXAMPLES 8 to 10

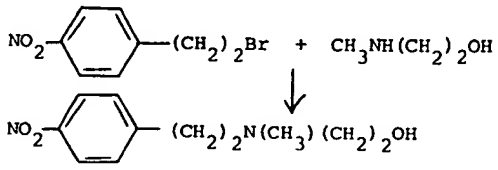
The following compounds were prepared similarly to the procedure of the previous Example parts (A) to (C), starting from corresponding starting materials except that in part (A) 2-(nitrophenoxy)ethyl bromides rather than chlorides were used, and were isolated in the forms indicated. The hydrochloride salts were prepared by dissolving the residue from the last evaporation step in ethyl acetate, adding ethereal hydrogen chloride, filtering off the resultant precipitate of the hydrochloride salt, followed by recrystallisation from the stated solvent:



Example No.	Y	Form Isolated	Recrystallization Solvent	m.p. (°C)	Analysis % (Theoretical in Brackets) C	H	N
8		Free base	60-80° Petroleum ether/ethyl acetate	113-4	51.9 (51.7	6.45 6.2	9.0 9.5)
9		Hydrochloride	Ethyl acetate/ methanol	178-80	47.7 (47.7	6.0 5.9	8.6 8.8)
10		Hydrochloride hydrate	Ethyl acetate/ methanol	185 (foams)	47.0 (47.1	6.1 6.3	8.0 8.2)

EXAMPLE 11

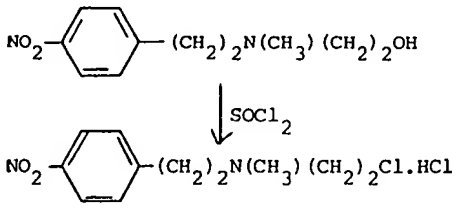
(A) 2-[N-Methyl-N-(4-nitrophenethyl)amino]ethanol



A mixture of 4-nitrophenethyl bromide (11.5 g) and N-methylethanolamine (8.25 g) in xylene (100 ml) was stirred at reflux for 16 hours. After evaporation, the residue was partitioned between 5% aqueous sodium bicarbonate and methylene chloride. The organic liquors were washed with saturated aqueous brine, dried ($MgSO_4$), filtered and evaporated to give an orange oil (10.1 g). Chromatography on silica ("Kieselgel 60" - Trade Mark) eluting with ethyl acetate followed by collection and evaporation of suitable fractions gave the title compound as a yellow oil, (7.5 g).

N.m.r. ($CDCl_3$) ppm, δ = 8.05 (d, 2H); 7.2 (d, 2H); 3.52 (t, 2H); 2.61 (m, 6H); 2.3 (s, 3H).

(B) 2-[N-Methyl-N-(4-nitrophenethyl)amino]ethyl chloride hydrochloride



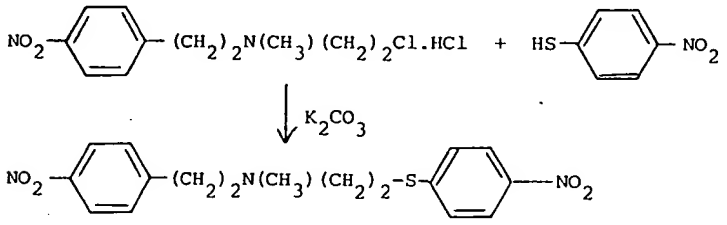
To a solution of 2-[N-methyl-N-(4-nitrophenethyl)amino]-ethanol (8.0 g) in dry methylene chloride (75 ml) was added dropwise thionyl chloride (3 ml) with stirring at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 16 hours. The resultant solid was filtered, washed with dry ether and dried to give a colourless product (7.1 g). Crystallisation from ethyl acetate/methanol gave the title compound, 6.0 g, m.p. 168-9°.

Analysis %:-

Found: C,46.8; H,5.8; N,9.85;

Calculated for $C_{11}H_{15}ClN_2O_2.HCl$: C,47.3; H,5.8; N,10.0.

(C) 2-[N-Methyl-N-(4-nitrophenethyl)amino]-1-(4-nitrophenylthio)ethane



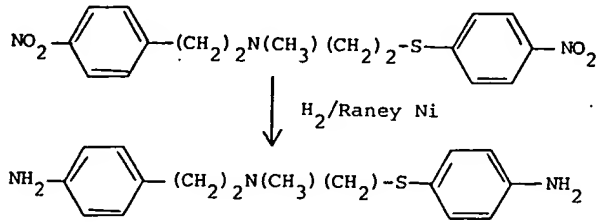
2-[N-Methyl-N-(4-nitrophenethyl)amino]ethyl chloride hydrochloride (3.0 g), 4-nitrothiophenol (1.7 g) and potassium carbonate (4.0 g) in acetonitrile (100 ml) were stirred at reflux for 16 hours. After evaporation, the residue was partitioned between water and ethyl acetate. The organic liquors were washed with saturated aqueous brine, dried ($MgSO_4$), filtered and evaporated to give an orange oil (3.6 g). Chromatography on silica ("Kieselgel 60" - Trade Mark) eluting with ethyl acetate followed by collection of suitable fractions gave on evaporation the title compound as a yellow solid, (3.05 g), m.p. 56-7°.

Analysis %:-

Found: C,56.8; H,5.3; N,11.7;

Calculated for $C_{17}H_{19}N_3O_4S$: C,56.5; H,5.3; N,11.6.

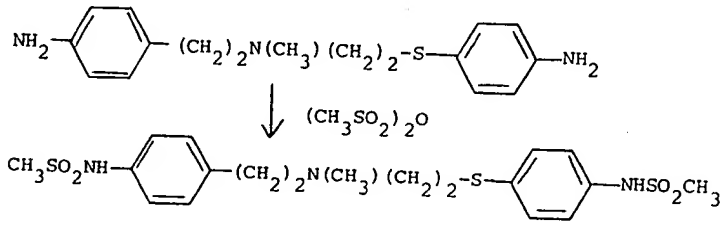
(D) 1-(4-Aminophenylthio)-2-[N-(4-aminophenethyl)-N-methylamino]ethane



The title compound was prepared by the hydrogenation of 2-[N-methyl-N-(4-nitrophenethyl)amino]-1-(4-nitrophenylthio)-ethane over Raney nickel according to the procedure of Example 7(B).

N.m.r. ($CDCl_3$) ppm, δ = 7.25 (d, 2H); 6.98 (d, 2H); 6.60 (m, 4H); 2.92 (t, 2H); 2.60 (m, 6H); 2.32 (s, 3H).

(E) 1-(4-Methanesulphonamidophenylthio)-2-[N-(4-methanesulphonamidophenethyl)-N-methylamino]ethane



The title compound, m.p. 160-3°, was prepared by the mesylation of the product of part (D) above using methanesulphonic anhydride according to the procedure of Example 7(C).

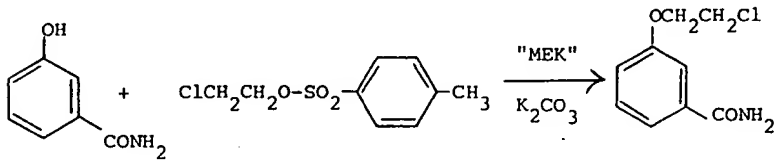
Analysis %:-

Found:	C,49.5; H,6.1; N,8.6;
Calculated for $C_{19}H_{27}N_3O_4S_3$:	C,49.9; H,5.95; N,9.2.

The following Preparations, in which all temperatures are in °C, illustrate the preparation of certain novel starting materials:-

Preparation 1

3-(2-Chloroethoxy)benzamide



To a solution of 3-hydroxybenzamide (21.6 g) in ethyl methyl ketone ("MEK") was added 2-chloroethyl p-toluenesulphonate (55.46 g) and potassium carbonate (16.0 g). After stirring at reflux for 6 hours, the resultant mixture was poured onto water and a colourless solid filtered off. Crystallisation from ethanol gave the title compound, (22.2 g), m.p. 125-126°.

Analysis %:-

Found:	C,53.7; H,5.3; N,6.9;
Calculated for $C_9H_{10}ClNO_2$:	C,54.1; H,5.05; N,7.0.

Preparation 2

2-(2-Chloroethoxy)-5-methylbenzamide

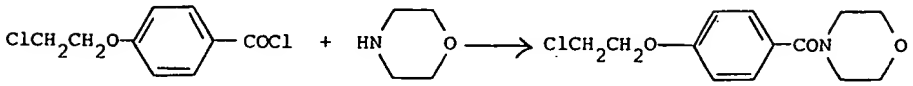
The title compound was made similarly to Preparation 1 from corresponding starting materials, m.p. 111-113°.

Analysis %:-

Found:	C,56.4; H,5.65; N,6.3;
Calculated for $C_{10}H_{12}ClNO_2$:	C,56.2; H,5.7; N,6.6.

Preparation 3

4-{4-[2-Chloroethoxy]benzoyl} morpholine



4-(2-Chloroethoxy)benzoyl chloride (5.0 g) was dissolved in dry methylene chloride and stirred while cooling to 0°. Morpholine (4.0 g) was added dropwise and the mixture was stirred at room temperature for 2 days. The resultant colourless solid was filtered off and the liquors allowed to stand from which the title compound crystallised (5.5 g), m.p. 102-4°.

Analysis %:-

Found:	C,58.1; H,6.0; N,5.25;
Calculated for $C_{13}H_{16}ClNO_3$:	C,57.9; H,6.0; N,5.20.

Preparation 4

N,N-Diethyl 4-(2-chloroethoxy)benzamide

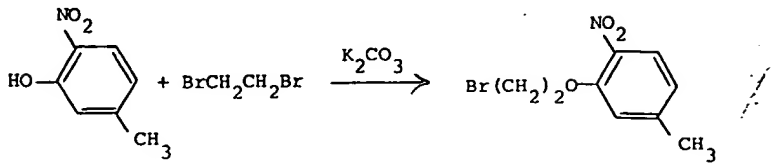
The title compound was prepared similarly to the previous Preparation from corresponding starting materials, m.p. 80-81°.

Analysis %:-

Found:	C,60.8; H,7.0; N,5.3;
Calculated for $C_{12}H_{18}ClNO_2$:	C,61.05; H,7.1; N,5.5.

Preparation 5

5-Methyl-2-nitrophenyl 2'-bromoethyl ether



5-Methyl-2-nitrophenol (5.0 g) and potassium carbonate (4.6 g) in butanone (100 ml) were stirred together at room temperature for 0.5 hours. 1,2-Dibromoethane (3.1 g) was then added and the mixture stirred at reflux for 2 days. After evaporation to dryness, distilled water was added and the mixture was extracted three times with methylene chloride. The combined organic liquors were washed with water, dried over magnesium sulphate, filtered and evaporated to give a yellow solid which was removed by filtration and the solution was evaporated to low bulk, giving the title compound as colourless crystals, m.p. 48-49°, used in Example 10.

N.m.r. ($CDCl_3$), ppm δ = 7.8 (d, 1H); 6.9 (m, 2H); 4.42 (t, 2H); 3.7 (t, 2H); 2.45 (s, 3H).

3-Nitrophenyl 2'-bromoethyl ether and 2-nitrophenyl 2'-bromoethyl ether used, respectively, as starting materials in Examples 8 and 9 are known compounds [see C.A., 59, 9883f and C.A., 61, 601a].

It will be appreciated from the foregoing that what we will claim may include the following:-

(1) The compounds of the formula (I) and their pharmaceutically acceptable salts;

(2) Processes as described herein for preparing the compounds of the formula (I) and their salts;

(3) Pharmaceutical compositions comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier;

(4) A compound of the formula (I) for use as a medicament; and

(5) The use of a compound of the formula (I), or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or reduction of cardiac arrhythmias.

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